



**[Billing Code 4140-01-P]**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**Government-Owned Inventions; Availability for Licensing**

**AGENCY:** National Institutes of Health

**ACTION:** Notice

**SUMMARY:** The inventions listed below are owned by an agency of the U.S. Government.

**FOR FURTHER INFORMATION CONTACT:** Licensing information may be obtained by emailing the indicated licensing contact at the National Heart, Lung, and Blood, Office of Technology Transfer and Development Office of Technology Transfer, 31 Center Drive Room 4A29, MSC2479, Bethesda, MD 20892-2479; telephone: 301-402-5579. A signed Confidential Disclosure Agreement may be required to receive any unpublished information.

**SUPPLEMENTARY INFORMATION:** The following inventions are available for licensing in accordance with 35 U.S.C. 209 and 37 CFR Part 404 to achieve expeditious commercialization of results of federally-funded research and development. Technology description follows.

**Methods for Improving Drug Delivery to the Central Nervous System**

The invention relates to the uses of the tricyclic antidepressant amitriptyline, its bioactive metabolites, and other LPA1R activators to improve the bioavailability and delivery of therapeutics to the central nervous system. This invention demonstrates that amitriptyline and other agents selectively decrease P-glycoprotein (P-gp) transport activity by ligand

activation of lysophosphatidic acid 1 receptor (LPA1R) at the blood-brain barrier. P-gp is an effective target for increasing drug delivery to the brain (CNS) for two major reasons: (1) its substrates include a large portion of on-the-market drugs, including chemotherapeutics, and (2) its directionality results in a net efflux of drugs from the brain. Additionally, specifically targeting P-gp through LPA1R activation bypasses the clinical challenges resulting from the toxicity of substrate inhibitors of P-gp. This invention describes the inhibition of drug efflux by P-gp transport; thus, co-administration of therapeutics with amitriptyline and other LPA1R activators provides a method for increasing drug delivery to the CNS, and improving overall drug efficacy. Moreover, drug delivery to other barrier tissues will also be enhanced where a similar LPA1R-P-gp activity relationship exists.

#### **Potential Commercial Applications:**

- Drug Delivery to the CNS
- Co-administration of therapeutics
- Blood-brain-barrier permeability

#### **Development Stage:**

- Early stage

**Inventors:** Ronald Cannon and David Banks (NIEHS)

#### **Publications:**

- Cannon et al., Neurosci Lett. 2017 Feb 3;639:103-113 doi: 10.1016/j.neulet.2016.12.049.

- Mesev, et al., Mol Pharmacol. 2017 Jan 24. pii: mol.116.107169. doi: 10.1124/mol.116.107169.
- More, et al., J Cereb Blood Flow Metab. 2016 May 18. pii: 0271678X16650216.
- Miller, et. al, Curr Pharm Des. 2014;20(10):1463-71. Review.
- Cartwright, et al. J Cereb Blood Flow Metab. 2013 Mar;33(3):381-8. doi: 10.1038/jcbfm.2012.174.

**Intellectual Property:** HHS Reference No. E-179-2065/0 and /1; U.S. Provisional Patent Applications 62/332,888 filed May 6, 2016, and 62/453,718 filed February 2, 2017, respectively.

**Licensing Contact:** Michael Shmilovich, Esq, CLP; 301-435-5019;  
shmilovm@mail.nih.gov

Dated: February 10, 2017

---

Michael Shmilovich  
Senior Licensing and Patenting Manager  
National Heart, Lung, and Blood Institute,  
Office of Technology Transfer and Development  
[FR Doc. 2017-03306 Filed: 2/17/2017 8:45 am; Publication Date: 2/21/2017]